

Cutaneous Manifestations of Diabetes Mellitus in Adult Patients of Telangana Region of South India

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Abstract: Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Although diabetes mellitus can be asymptomatic, many patients present with wide spectrum of manifestations. The untreated hyperglycemia of diabetes can cause many acute and serious long term complications. DM is frequently associated by a variety of cutaneous manifestations that commonly serve as ports of entry for different microorganisms. Skin manifestations can be associated with both type 1 & type 2 Diabetes and were seen in patients who use insulin as well as those who use oral hypoglycemic agents to control their glucose levels. Early recognition of these skin manifestations assists in early diagnosis and helps to lead towards appropriate treatment for diabetes mellitus patients. Early diagnosis also helps in preventing long-term complications. The present study evaluates the frequency of skin manifestations in 220 diabetic patients of Telangana region of south India. Skin infection (19.35%), itching (12.09%), & skin atrophy (10.48%) are the three most common initial skin manifestations in DM patients. The present study reveals that it took more than 10 years for skin manifestations to appear in 60% of the patients. On the other hand, no patient reported manifestations at 30 or more years since they have been diagnosed with DM. The maximum number of patients who reported skin manifestations was at 17-18 years since the onset of DM diagnosis.

Keywords: Diabetes mellitus, hyperglycemia, itching, infection, skin manifestations

1. Introduction

Diabetes mellitus is an emerging global health problem. It is a chronic, noncommunicable, and expensive public health disease.

Wild et al. [1] reported that in the year 2000, there were about 171 million diabetes mellitus cases worldwide in patients aged 20 years or more, 17 million of these cases were found in the United States of America, making the US the third highest country in the prevalence of Diabetes mellitus after India and China. In 2010, the International Diabetes Federation [2] reported a diabetes prevalence of 12.3% in the US and 7.8% in Iraq.

In 2011 diabetes resulted in 1.4 million deaths worldwide, making it the eighth leading cause of death [3].

Globally, in year 2013, an estimated 382 million people had diabetes worldwide, with type 2 diabetes making up about 90% of the cases [4], this is equal to 3.3% of the population, with equal rates in both women and men [5] and the number of people with diabetes is expected to rise to 592 million by 2035 [6]. In India, year 2013, an estimated 65.1 million people had diabetes and it will reach up to 109.0 million in year 2035.

This study also aims at showing the prevalence of individual Diabetes skin manifestations in relation to gender, length of years since the diagnosis of Diabetes Mellitus and response to treatment.

1.1 Skin Manifestations in Diabetes Mellitus

Cutaneous manifestations of Diabetes Mellitus are common and frequently serve as ports of entry for different micro-organisms. Exposure to such micro-organisms might result in secondary infections. Patients with type 1 DM are commonly presented with autoimmune-related skin manifestations such as Vitiligo, Lichen planus, etc., while patients with type 2 DM typically develop skin **manifestations** like thick skin, Granuloma annulare, etc. Unfortunately, some cases of DM stay undiagnosed until complications appear. Moniliasis can be an early sign of such cases as reported by Van Hattem et al [7].

2. Material and Methods:

This was a prospective, longitudinal, single center study conducted by the Department of Medicine at Chalmeda Anand Rao Institute of Medical Sciences, a semi-urban tertiary care teaching hospital – Bommakal village-Karimnagar district- Telangana - India, over a period of three years from March 2011 to March 2014. The aim of the present study is to find out prevalence of cutaneous manifestations of DM in adults patients of Telangana

region of South India. During the study period we enrolled 400 diabetic patients (192 males and 208 females), among them, only 220 patients had skin manifestations. Diabetic adult patients (age range from 20 to 75 years): newly detected, admitted cases in medical ward & who are coming for follow up in OPD were included.

All patients underwent detail history and physical examination. Demographic data are recorded such as: name of the patient, age, gender, education, dietary habit, income, type of family, family history of chronic diseases, race, occupation, type of DM, approximate date or year of onset of DM, the treatment he/she received and when the given treatment started, his/her response to the treatment, what was the first, second and third cutaneous manifestation he/she observed and in what chronological order, was their DM controlled. Head to toe physical examination was performed with all patients including searching the clinical skin manifestations related to diabetes mellitus. After full examination of the patients skin manifestations related to DM were reported and documented. Venous blood was also collected to measure plasma glucose level and diabetes was diagnosed according to WHO diabetes diagnostic criteria (Table 1 & 2).

Table 1: WHO criteria for diagnosis of DM

Condition	2 hour glucose, mmol/l (mg/dl)	Fasting glucose, mmol/l (mg/dl)	HbA1 C (%)
Normal	<7.8 (<140)	<6.1 (<110)	<6.0
Impaired fasting glycemia	<7.8 (<140)	≥6.1 (≥110) &<7.0 (<126)	6.0- 6.4
Impaired glucose tolerance DM	≥ 7.8 (≥ 140)	<7.0 (<126)	6.0- 6.4
	≥ 11.1 (≥200)	≥7.0 (≥126)	≥6.5

[DM diagnosed by demonstrating any one of the following: (1) Fasting plasma glucose level ≥ 7.0mmol/l(126mg/dl),(2) plasma glucose level ≥ 11.1mmol/l(200mg/dl),two hours after a 75g oral glucose load as in a GTT,(3) Symptoms of hyperglycemia &casual plasma glucose ≥ 11.1mmol/l(200mg/dl), & (4)HB A1C ≥6.5%.]

Table 2: Screening for diagnosis of GDM

Perform a 75g OGTT, with a plasma glucose measurement on fasting and at 1 and 2hours, at 24-28 weeks of gestation in women not previously diagnosed with overt diabetes. The OGTT should be performed in the morning after an overnight fast of at least 8 hours
The diagnosis of GDM is made when any of the following plasma glucose values are exceeded: (1) Fasting: ≥ 5.1mmol/l (≥ 92mg/dl),(2) 1h: ≥ 10.0mmol/l(≥ 180mg/dl),& (3)2h: 8.5mmol/l(≥ 153mg/dl).

3. Results:

The collected data was formed in tables. Table 3 shows both the absolute frequency (patients) and the corresponding relative frequency of the various skin manifestations related to Diabetes mellitus.

Skin infections were present in 96 patients representing 19.35% from all observed skin manifestations. Skin infections prevalence was followed by itching, which was noticed in 60 patients representing 12.09% of the observed skin manifestations (Table 3).

Table 3: Frequency of cutaneous manifestation in adult DM patients in present study

<i>Cutaneous Manifestations</i>	<i>Absolute frequency (Patients)</i>	<i>Relative frequency (%)</i>
Infections	96	19.35
Itching	60	12.09
Skin atrophy, interdigital Maceration	52	10.48
Waxy skin	48	9.67
Lipodystrophy	48	9.67
Skin itching	36	7.25
Sweating disturbance	36	7.25
DM dermopathy	32	6.45
Yellow nail	32	6.45
Ulcer	16	3.22
Carotenosis	16	3.22
DM Microangiopathy	12	2.41
Necrobiosis lipodica	4	0.80
Digital sclerosis	4	0.80
Xanthelasma	4	0.80
Others (Granuloma annulare, Acanthosis nigricans, Wet gangrene of foot, Vitiligo, etc.)	0	0
Total number of manifestations in the 220 patients	496	200

Different types of infections observed in diabetic patients involved in this study are shown in Table 4 .It is quite obvious from Table 4 that Folliculitis predominates, while Tinia infections has low prevalence. There were 160 manifestations caused by bacterial origin, including folliculitis, boil, abscess, cellulites and erysipelas representing a total of 64.51% of the observed skin infections. From the observed skin infections, there were 56 candida infections which represented 22.58% of total observed skin infections (Table 4).

Table4: Different types of Infections in the present study.

<i>Skin manifestations</i>	<i>Absolute frequency (Manifestations)</i>	<i>Relative frequency (%)</i>
Folliculitis	68	27.41
Candida	56	22.58
Boil	36	14.51
Abscess	20	8.06
Cellulites	20	8.06
Viral	20	8.06
Erysipelas	16	6.45
P. Versicolor	8	3.22
Tineas	4	1.61
Total	248	100

Prevalence of the first cutaneous manifestation to appear in DM patients is shows in Table 5. Infections are first commonest cutaneous manifestation followed by Folliculitis, Boil, abscess etc., and rare manifestations are Lipodystrophy & Waxy skin (Table5).

Table 5: First manifestations to appear in DM patients in our study.

<i>Skin manifestations</i>	<i>Absolute frequency (Manifestations)</i>	<i>Relative frequency (%)</i>
Infections	96	43.63
Folliculitis	40	18.18
Boil	16	7.27
Abscess	16	7.27
Cellulites	16	7.27
Candida	8	3.63
Itching	92	41.81
Sweating disturbances & Skin atrophy	8	3.63
DM dermopathy	8	3.63
Ulcer	8	3.63
Lipodystrophy	4	1.81
Waxy Skin	4	1.81

Table 6 shows that it took more than 10 years for skin manifestations to appear in 132 patients (60%). On the other hand, no patient reported manifestations at 30 or more years. Although skin manifestations can be observed early, some skin manifestations can take 20 to 25 years till they appear. It is also obvious that the maximum number of patients with skin manifestations was reported at 17-18 years of the diagnosis of DM.

Patients used	96	43.63
OHA		
Patients used	124	56.36
Insulin		
Total	220	100

Table 6: Number of year’s diabetes started before the appearance of cutaneous manifestations.

Number of Years (patients)	Absolute frequency	Relative frequency (%)
5	44	20.00
10	44	20.00
15	48	21.81
20	48	21.81
25	36	16.36
30	0	0
Total	220	100

Other data that was obtained from present study; included type of DM, response to treatment; type of treatment (oral hypoglycemic agents “OHA” or insulin) is presented in Table 7.

Table 7: Effect of DM control on skin manifestations.

Status of DM control	Absolute frequency (Patients)	Relative frequency (%)
Controlled DM	160	72.73
UN-Controlled DM	60	27.27
Total	220	100

Although many patients had good response to treatment, some still had a lot of cutaneous manifestations. Most of them were type 1 DM. Patients who were using OHA reported less skin manifestations than those who were on insulin (Table 8).

Table 8: Factors affecting DM skin manifestations prevalence.

	Absolute frequency (Patients)	Relative frequency (%)
<i>Effect of response to treatment on DM cutaneous manifestation prevalence</i>		
Good response	180	81.81
Poor response	40	18.18
Total	220	100
<i>Effect of DM type on cutaneous manifestation prevalence</i>		
Type 1 DM	124	56.36
Type 2 DM	96	43.63
Total	220	100
<i>Effect of treatment modality on DM cutaneous manifestation prevalence</i>		

4. Discussion:

Diabetes mellitus is a common disorder and nearly all individuals with diabetes might develop skin manifestations. Many of these manifestations might be explained on the basis of the attachment of glucose to proteins and the subsequent metabolism of this combination, which causes changes in structure, function and color.

4.1 Types of Diabetes Mellitus

According to WHO, DM is classified in to three main types and others types. (1) Type 1 DM, (2) Type 2 DM, (3) Type 3 {GDM} & (4) Other types. Table 9 shows complete classification of DM. Assigning a type of diabetes to an individual often depends on the circumstances present at time of diagnosis, and many diabetic individuals do not easily fit into a single class. For example, a person with GDM may continue to be hyperglycemic after delivery and may be determined to have , in fact, type 2 DM. Alternately , a person who acquires diabetes because of large doses of exogenous steroids may become normoglycemic once the glucocorticoids are discontinued, but then may develop DM many years later after recurrent episodes of pancreatitis. Another example would be a person treated with thiazides who develops DM years later. Because thiazides in themselves seldom cause severe hyperglycemia, such individuals probably have type 2 DM that is exacerbated by drugs. Thus, for the clinician & patients, it is less important to label the particular type of DM than it is to understand the pathogenesis of hyperglycemia and to treat effectively.

Table 9: Types of DM (Etiological classification of DM)

Type 1DM (IDDM or Juvenile DM): Characterized by loss of insulin producing β -cells of the islets of Langerhans in the pancreas, usually leading to absolute insulin deficiency. This type can be further classified as: Immune –mediated & Idiopathic.
Type 2 DM (NIDDM or adult-onset DM): Characterized by insulin resistance which may be combined with relatively reduced insulin secretion.
Type 3 DM (GDM): It resembles type 2 DM in several aspects, involving a combination of relatively inadequate insulin secretion and responsiveness.
Other type DM:
(1) Genetic defects of β -cells function – MODY & Mitochondrial DNA mutations.
(2) Genetic defects in insulin processing or insulin action – Defect in proinsulin conversion, Insulin gene mutations & Insulin receptor mutations.
(3) Exocrine pancreatic defects – Chronic pancreatitis,

Pancreatectomy, Pancreatic neoplasia, Cystic fibrosis, Hemochromatosis, & Fibrocalculous pancreatopathy.
 (4) Endocrinopathies – Growth hormone excess (acromegaly), Cushing syndrome, Pheochromocytoma, Glucagonoma, & Hyperthyroidism.
 (5) Infections – Cytomegalovirus infection, Coxsackievirus B, Adenoviruses & Mumps
 (6) Drugs – Glucocorticoids, Thyroid hormone, β -adrenergic agonists, & Statins.

(Drugs induced DM: the list shown in this table is not all-inclusive, but reflects the more common recognized drugs, hormones, or toxin induced form of DM)

4.2 Biochemical Considerations in DM

Diabetes mellitus comprises a group of common metabolic disorders that share the phenotype, hyperglycemia. Depending on the etiology of DM, many factors might cause hyperglycemia, including reduced insulin secretion, decrease glucose usage and increased glucose production.

The process of non-enzymatic glycosylation occurs to a minor extent at normal blood sugar concentrations. This gradual glycosylation of proteins may be responsible for some of the skin changes associated with aging. This process is apparently accelerated in persons with elevated blood sugars. Most proteins evaluated seem to be involved by this reaction which results in changes in the physical and chemical properties. According to Druggly [8], the glycosylation of the red cell membrane is apparently responsible for the stiffness of diabetic erythrocytes.

4.3 Clinical Features of DM

Diabetic patients may be either asymptomatic or presented with skin turgor, dry furred tongue, cracked lips, tachycardia, hypotension, polyuria, polydipsia, increased intracranial pressure symptoms, harsh acidotic breathing, mental apathy, confusion and coma. Fatigue and recurrent infections like fungal infection are not uncommon. Symptoms due to ketosis are expressed through vomiting and abnormal smell. Diabetic retinopathy can be simple, pre-proliferative or proliferative. Diabetic neuropathy can be sensory, motor, mononeuritis or autonomic with impaired reflexes. Diabetic nephropathy expressed through leg edema, proteinuria and accelerated arteriosclerosis.

4.4 Pathogenesis of DM

Insulin is the principal hormone that regulates the uptake of glucose from the blood into most of the cells, especially liver, muscle, and adipose tissue. Therefore deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of DM.

Several pathogenic processes are involved in the development of DM. These range from autoimmune destruction of the β -cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, & protein metabolism in diabetes is due to deficient action of insulin on target tissue. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia.

4.5 Cutaneous manifestations in the present study

According to our findings; skin infections (19.35%), itching (12.09%) & skin atrophy (10.48%), are the three most common initial presentations in diabetes patients. Some patients reported other initial manifestations, such as: ulcer, waxy skin, etc.

Waxy skin was seen in 1.81% of the patients which was less than the results shown by Huntley A, 10% and this may be related to the differences in the genetic and the racial causes of DM.

Diabetic dermopathy was seen in 3.63% of the patients in this study which was less than the 14% obtained by Huntley A and Murphy [9]. Morgan and Schwartz[10] reported Diabetic Dermopathy as the most common cutaneous manifestation of DM in the US. The low prevalence of diabetic dermopathy in this study may be related to the availability of free health care, which might be contributed to an early diagnosis and prevention of chronic complications.

Skin ulcer was seen in 3.63% of the patients of this work which is in agreement with the 5% given by Freedberg [11]

Cutaneous manifestations started to appear in different intervals after the onset of DM ranging from 5 to 25 years. There were no substantial differences between male and female incidences of cutaneous manifestations in Telangana region of south India as it appeared in 52% females and 48% males. This is in agreement with the study performed by Ahmed et al [12] who reported that 55.1 % were females and 44.9% were males.

The incidence of DM I in those with skin manifestations was 56.36%, Druggly R reported a prevalence of 12% as insulin-dependent diabetes mellitus. The incidence of DM II was 43.63% in this study as compared with 25% reported by Al-Masommi [13].

In the present study, about 56.36% of the patients having skin manifestation were on insulin, which was close to the 62% reported by Khan [14] and Kennedy et al [15]. Glucose level control doesn't significantly affect the prevalence of the skin

manifestations. 160 patients (72.72%) developed skin manifestations, although their glucose levels were well controlled.

5. Conclusions:

The main conclusions and recommendations of this work can be summarized as follows: (1) Cutaneous manifestations are fairly common among patients complaining of diabetes mellitus. The most common cutaneous manifestations seen in DM patients are bacterial and other skin infections.(2) The appearance of the cutaneous manifestation is affected by Chronicity.(3) Cutaneous infection, itching, and skin atrophy are the most common three initial skin manifestations in Diabetes Mellitus patients of this work.(4) The maximum number of patients with skin manifestation was observed 17-18 years after the onset of diabetes mellitus in the participants.(5) There is no substantial difference between males and females in the incidence of the cutaneous manifestations.(6) It is recommended to focus the attention to the primary skin manifestations as it may lead to the diagnosis of DM.(7) The limitations of our study were, less number of patients were included and this is a single center study, and findings may not be generalized to different populations and it requires multicenter study.(8) It is recommended to educate the patients regarding glucose level control, compliance with medications, and skin hygiene.

6. Abbreviations:

DM: Diabetes mellitus, IDDM: Insulin dependent DM, NIDDM: Non-Insulin dependent DM, GDM: Gestational DM, HbA1C: Glycated hemoglobin, OGTT: Oral Glucose tolerance test, MODY: Maturity onset diabetes of the young,

Acknowledgements

The authors thanks to our research committee of CAIMS, for permission to publish this manuscript.

8. Conflict of Interest: None declared.

9. Funding: No funding source.

10. Ethical approval: The study was approved by institutional ethics committee.

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